Post-traumatic stress disorder

In this section, the scientific and societal impact of my research will be clarified.

Scientific impact

Although post-traumatic stress disorder (PTSD) is a highly debilitating psychiatric disorder, no medical tools are currently available to prevent or minimize the impact of traumatic stress on mental health. Moreover, PTSD remains difficult to treat, with the only currently FDA-approved pharmacological treatment options being two antidepressants [1]. There is thus a pressing need to identify precise (neuro)biological mechanisms mediating risk and resilience to the effects of traumatic stress in order to better understand its biological basis, which in turn could lead to more optimal treatment strategies.

The studies presented in this thesis aim to unravel biological underpinnings of PTSD, some using novel study designs. For example, sequencing the microRNA (miRNA) content of human blood and urine neuron-derived exosomes has not been done yet so far. Chapters 6 therefore presents some of the first studies assessing such miRNA profiles using limited amounts of starting material. Studies like these, along with the optimized protocol needed to analyze these miRNAs, which is presented in Chapter 5, contribute to establishing the scientific foundation this field needs by striving for more standardization. Next, using longitudinal DNA methylation data as opposed to cross-sectional data only is another relatively unexplored and novel avenue representing an interesting advancement in the field by yielding potentially more specific methylation patterns due to correcting for pre-existing differences. The study presented in Chapter 7 is among the first to perform these type of analyses in relation to PTSD.

The generated data can now be embedded within larger systems biology efforts aiming to combine several biological layers in order to deepen our understanding of PTSD. This highlights the scientific relevance of the present studies, even though the findings should be regarded as preliminary and are in need of future replication and validation using larger study cohorts. The acquired knowledge could further give rise to a range of follow-up studies, including functional analyses of the identified miRNAs, *in silico* studies to predict miRNA-messenger RNA (mRNA) interactions, *in vitro* studies using patient-derived cells in order to observe dynamic cellular behavior upon administration of stress-related (exosomal) miRNAs, and extrapolation of the findings to other cohorts in order to verify overlap with stress-related disorders other than PTSD. Moreover, as epigenetic modifications are in principle reversible, robust alterations could prove to be interesting targets for therapeutic interventions in the future.

Anticipated societal impact

The economic burden of PTSD is substantial [2]. Since trauma exposure is close to inevitable in certain populations such as deployed military members, the prevalence of PTSD among war veterans is far greater than in the general population [3]. The symptoms associated with PTSD prevent suffering individuals from leading a healthy lifestyle and are debilitating on a personal, societal as well as a professional level [4]. Since establishing a PTSD diagnosis is mostly based on self-reported symptoms, this thesis encourages the development of a biological test in order to obtain a more precise and accurate reflection of PTSD status. As mentioned before, while returning military members are at high risk of developing PTSD, the current stigma associated with mental health disorders could prevent some of them from seeking appropriate healthcare [5]. Moreover, with PTSD being classified as a "mental" health disorder, they may not be willing to fully disclose their symptoms out of concerns for other people's opinions or job-related consequences. Therefore, and given the added difficulty of diagnosing PTSD given its complexity and high rates of co-morbidities, using objective biomarkers would be highly beneficial as an addition to post-deployment clinical assessments. Identifying such a marker could then encourage suffering individuals to seek treatment faster, and optimize their chances of returning to a "normal" lifestyle as soon as possible, thereby going back to contributing to society. Importantly, although not addressed directly here, the search for such a biomarker should go alongside efforts aiming to destigmatize disorders such as PTSD and change the narrative surrounding mental health disorders in general, which is especially crucial in populations such as the veteran population.

At this stage, the findings presented in this thesis are still too preliminary to result in any concrete, finished or clinically usable product. However, once validated, replicated, and perhaps embedded within a broader network of biological dysregulations associated with PTSD, the identified epigenetic markers could hold potential to serve as diagnostic biomarkers. Their presence in blood further makes them ideal biomarker candidates given the relative ease with which blood can be drawn. Additionally, examining the utility of using such markers as predictors of treatment response on an individual level could be interesting in yielding recommendations for personalized treatment strategies. However, this has to be viewed in light of the current limitations of identifying psychiatric biomarkers, as detailed in Chapter 8.

The populations that would benefit from the research presented in this thesis, are military members returning from combat, or individuals with similar high-risk professions.

Inversely, for military members who are about to be sent out, resilience studies presented in this thesis show that several preventive (cognitive) interventions could be implemented during pre-deployment preparation periods in order to increase one's psychological resilience. Gaining deeper insights into the biologic basis of resilience and resilience-promoting approaches such as mindfulness, could lead us to develop personalized preparation steps and/or treatment plans, potentially by combining psychotherapeutic strategies and pharmacological treatments precisely aimed at targeting resilience-promoting pathways [6].

Although the search for psychiatric biomarkers is steadily increasing, practical, societal or even legal implications of using and interpreting such biomarkers, have been given little attention. As discussed by Lehmer and Yehuda (2014) [5], the search for a PTSD biomarker should be accompanied by interdisciplinary discussions in order to understand how to best incorporate potential biomarkers within clinical settings. Undoubtedly, bioethicists should join the conversation in order to weigh in on the ethical implications of using such markers. Importantly, the complexity of PTSD should under no circumstances be reduced to the mere presence or absence of certain markers. How to best understand and use biomarkers to benefit suffering individuals, and how this information should be translated to society, needs critical attention. Similarly, the extent to which biomarkers developed for combat-related PTSD in the military will be applicable to civilian populations, will also need further examination [7].

References

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